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㉖ Controlled release formulations.

㉗ Active substances intended for topical application are incorporated in novel formulations in which they are retained as impregnants inside the pores of porous solid particles or microspheres. The pores form a continuous network open to the exterior of the particles, permitting outward diffusion of the impregnants at a controlled rate depending on the pore size. The impregnated particles are prepared by the polymerization of monomer droplets which contain the active substance mixed in with the monomers, or by impregnation of preformed particles with the active substance.

**EP 0 306 236 A2**

## CONTROLLED RELEASE FORMULATIONS

BACKGROUND OF THE INVENTION

5 The present invention relates to controlled release compositions comprised of porous polymeric microbead carriers retaining within their pores various types of impregnants. In a first aspect, the impregnants are topical formulations useful in the promotion of hair growth. In a second aspect, the impregnants are topical compositions used in the treatment of acne. In a third aspect, the impregnants are fragrant compositions. In a fourth aspect, the impregnants are vitamins and vitamin derivatives. In a fifth aspect, the impregnants are counterirritants. In a sixth aspect, the impregnants are epidermal lipid replacement substances. The invention further relates to methods of preparing such compositions and their methods of use.

1.1 Topical Formulations for the Promotion of Hair Growth

Minoxidil has recently been reported to exhibit beneficial properties for the promotion of hair growth. See, e.g., U.S. Patent No. 4,139,619, the disclosure of which is specifically incorporated herein by reference. Minoxidil is a piperidinopyrimidine and is described in the Merck Index (10th Edition) published by Merck & Co., Inc., Rahway, New Jersey at pages 888-889, the disclosure of which is specifically incorporated herein by reference. While Minoxidil is packaged in a tablet or capsule for use in the treatment of hypertension, a delivery vehicle for the topical application to a skin surface is needed. In order to maximize the benefit of such application, the vehicle should allow absorption through the skin surface to which it is applied. Additionally, it would be preferable to provide a time release mechanism for absorption of the active ingredient.

1.2 Topical Compositions used in the Treatment of Acne

30 Acne is a pleomorphic skin disease characterized by blackheads, whiteheads, papules, pustules, cysts, and various sized nodules and scars which, in the inflammatory stage of the disease, are contaminated with bacteria such as *Propionibacterium acnes*. The disease involves the pilosebaceous units of the dermis which consist of the sebaceous follicle which include the sebaceous glands and ducts and small hairs.

Sebum (skin oil) is a complex mixture of fats and waxes liberated by the breakdown of the sebaceous cells. The production of sebum is intimately associated with the pathology of acne. Obstruction of the opening of the sebaceous follicle by a comedone, a solid horny mass or plug made up of keratinized cells and commonly referred to as whiteheads or blackheads, may block or stagnate sebum flow through the sebaceous follicle. This blockage leads secondarily to rupture of the follicular contents (sebum) into the dermis, and then to perfolliculitis. This provokes an inflammatory response which leads to the formation of pustules (pimples) when the rupture is small, and cystic nodules with complete rupture. A scar may eventually form, dependent on the depth and extent of the inflammatory response.

45 Benzoyl peroxide is an oxidizing agent believed to be one of the most effective topical nonprescription medications available for acne. Benzoyl peroxide is one of several topical agents used in treating acne to cause irritation and desquamation, thereby preventing closure of the pilosebaceous orifice. Salicylic acid is a known keratolytic and antibacterial agent also used in the treatment of acne.

Benzoyl peroxide is soluble in nearly all organic solvents, slightly soluble in alcohols and slightly soluble in water. It has a melting point of 103°C to 105°C and a specific gravity of 1.3340 at 25°C. Salicylic acid has a melting point of 158-161°C and a specific gravity of 1.443 (20/4°C). Salicylic acid is soluble in acetone, alcohol, ether and benzene, and slightly soluble in water.

50 The irritant effect of these peeling agents causes an increased turnover rate of epithelial cells lining the follicular duct, which increases sloughing. The desired effect is to reduce the tendency of the skin to form new comedones and to loosen the structure of the formed comedones and aid in their extrusion.

In the past, benzoyl peroxide has been administered to the skin in the form of gels, creams, lotions or ointments in concentrations of 2.5%-5.0% and 10%. There are several disadvantages to prior methods of delivering benzoyl peroxide to affected areas. Strong concentrations of benzoyl peroxide cannot be used

because high concentrations of the topical agent can cause localized reactions such as stinging and burning. Benzoyl peroxide is also a strong bleaching agent, and can permanently discolor sheets, pillowcases, towels, clothing or any other colored textiles if a liquid or gel containing the agent is spilled or otherwise contacts such articles.

- Problems have been encountered in attempting to combine salicylic acid with benzoyl peroxide. These problems are detailed in U.S. Patent No. 4,514,385, issued April 30, 1985 to Damani et al. Damani et al. suggests dispersing or suspending finely divided particles of benzoyl peroxide and salicylic acid in a particular class of aqueous carboxy vinyl polymer (carboxypolymethylene) gels in the absence of alkaline neutralizing agents which would tend to react with salicylic acid. The resulting products, characterized as creamy gels, are applied topically or in toiletries such as shampoos, soap bars and detergent bars used in washing the skin.

### 1.3 Fragrance Compositions

- The term "fragrance" embraces a heterogeneous group of substances capable of releasing vapors which impart sensation (usually pleasant) to the olfactory senses. Fragrances may be natural or synthetic compounds, including natural oils, e.g., flower oils, isolates from oils, animal products such as musk and ambergris, resins, balsams, and the like. Fragrances may be used in solutions as perfumes or colognes, or may be added to a wide variety of products, such as cosmetics, soaps, paper products, and the like.

- The addition of fragrances to other products is problematic. The fragrance substance to be added is frequently incompatible with the product in some manner. For example, many fragrances will react with the fatty acids present in soaps, resulting in discoloration of the product. Moreover, many fragrances are light sensitive and will degrade when exposed to sunlight, and fragrances are frequently sensitive to pH, and many classes of products have only a limited number of fragrances which are acceptable. Finally, fragrances are highly volatile by nature and are subject to rapid depletion.

- For these reasons, it would be desirable to provide fragrance compositions which are not subject to the limitations set forth above. In particular, it would be desirable to provide fragrance compositions which are compatible with a wide variety of products, regardless of the product pH, ionic affinity, and chemical composition. Such compositions should lessen the sensitivity of particular fragrance substances to light so that the compositions may be exposed to sunlight without substantial degradation, and the compositions should prolong the release of the fragrance over an extended time period without substantially altering the olfactory characteristics of the fragrance.

### 1.4 Vitamins and Vitamin Derivatives

- Vitamins are chemically unrelated, fairly complex organic substances that are essential in small amounts for the maintenance of normal metabolic functions. Vitamins are not synthesized within the human body and must therefore be furnished from exogenous sources. Natural sources of vitamins include plant and animal tissue.

- Vitamins can be broadly categorized as either fat-soluble or water-soluble. Vitamins A, D, E and K are fat soluble and are absorbed in association with lipids. Vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>5</sub>, B<sub>12</sub>, B<sub>15</sub>, B<sub>17</sub>, C, niacin, folic acid, pantothenic acid, biotin, bioflavonoids, choline, inositol and F are examples of water-soluble vitamins.

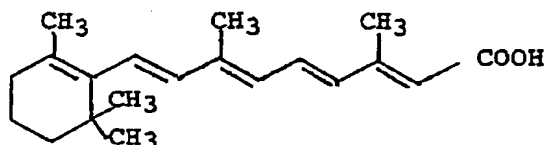
- Vitamins A, D and E, and derivatives thereof, including esters such as vitamin A palmitate, vitamin E acetate and vitamin E palmitate and substances which contain such vitamins and vitamin derivatives, such as fish oils, have long been known to be useful for various topical therapeutic and cosmetic purposes. Creams, ointments and powders containing vitamins A and D as such or in cod liver oil have been used for the prevention and treatment of prickly heat and diaper rash in infants. Vitamin E and vitamin E esters, such as the acetate and palmitate, have been used, typically in creams, ointments, lotions, oils and other cosmetic formulations, as skin moisturizers and smoothers, to treat chronic skin diseases, to aid in healing burns and wounds, to reduce scarring from wounds, as topical anti-inflammatory agents, and to protect the skin from damage from ultraviolet rays.

- Vitamin-containing therapeutic and cosmetic creams, ointments, lotions, oils and like formulations feel greasy or oily when applied, and often leave residues which are difficult to remove from the skin. Vitamin-containing powder preparations enable only limited amounts of vitamin to penetrate the skin.

Vitamins are also used as additives in preparations primarily intended for purely cosmetic use, such as lip balms, lipsticks, blushers, eyeshadows and foundations.

Retinoids are a group of compounds consisting of vitamin A and its analogs. In addition to their effectiveness in enhancing vision and fertility, the compounds in this group are effective as keratolytic agents, and as such are used topically to retard and ameliorate photoaging of facial skin and senile keratosis, to treat acne vulgaris, and to treat warts.

Vitamin A itself is a term used to designate several biologically active compounds, principally the alcohols retinol, whose chemical name is 3,7-dimethyl-9-(2,6,8-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenol, and 3-dehydroretinol. Other retinoids include the corresponding acids, aldehydes, esters and aromatic derivatives of these. The most common of the acids is retinoic acid, or 3,7-dimethyl-9-(2,6,8-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid, which has the structural formula:



This formula shows the all-trans-form, which is also known by the common name tretinoin. Other acids within the class include the 9,10-cis-form and the 13-cis-form. Examples of esters are the methyl ester and the ethyl ester. The acids are crystalline under ambient conditions, soluble in fats and alcohols. The esters are liquids under ambient conditions. The acids and their derivatives are of particular interest for their high therapeutic value.

For topical application, retinoids are typically formulated as creams, ointments, oils and the like. In such formulations, however, retinoids rapidly degrade and lose activity. In addition, moderate to severe skin irritation frequently results from the use of these formulations. Still further, these formulations usually feel oily or greasy when applied, and tend to leave residues on the skin which are difficult to remove.

### 1.5 Counterirritants

Counterirritants are topically applied substances used as pain relievers. They are applied to the intact skin to stimulate cutaneous receptors to induce sensations of warmth, which serve as a distraction from deep seated pain in areas such as muscles, joints and tendons. The effect of counterirritants is achieved by producing a mild, local inflammatory reaction, and the site of application is the skin surface adjacent to the actual source of pain. The theory behind the use of counterirritants in general is that the sensations brought about by the counterirritant itself, such as massage and warmth, crowd out the perception of pain from the adjacent pain source.

The type and intensity of response produced by the counterirritant depends on the particular counterirritant used, its concentration, the form in which it is applied, and the length of time it is left in contact with the skin. The actual mode of action varies among counterirritants, some causing redness (i.e., rubefacients) and irritation, others producing cooling sensations, and still others characterized as vasodilators.

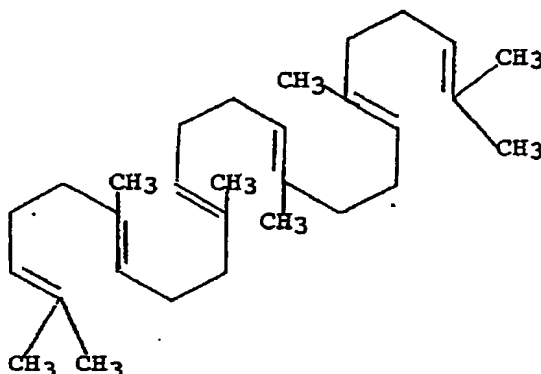
Counterirritants are generally formulated in liquid forms such as liniments and lotions or semisolid forms such as gels or ointments. In each case, the active ingredients are dissolved or dispersed in solvents or carrier vehicles which place the active ingredients in direct contact with the skin to produce immediate penetration. Dosages are set according to recommended limits by the concentrations of the active materials in the formulations, and by the frequency of application.

The reason for these dosage limitations is that counterirritants give rise to a number of undesirable side effects when used in high concentrations. These include ulcerations of the skin, rashes and blisters, dryness and fissuring of the skin, depending on the particular counterirritant used. In addition, certain species are systemically toxic. Further species are volatile and produce irritating vapors. For these reasons, regulations pertaining to the use and labeling of counterirritants as well as practical considerations impose limits on their concentrations and the frequency with which they should be applied. In many cases, this limits the effectiveness of these preparations, since their rapid penetration into the skin upon application causes a high initial effect, followed by a rapid decrease as diffusion proceeds. The decline in localized concentration and hence counterirritant effect is similar to that of a first order chemical reaction.

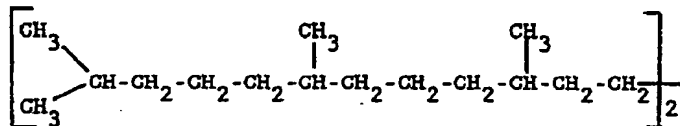
### 1.6 Epidermal Lipid Replacement Substances

Squalane and squalene are oils used as replacements for the natural epidermal lipids of the skin, which become depleted due to aging and general conditions of skin dryness. These oils are used for pharmaceutical and cosmetic purposes, and are applied directly to the skin, reconstituting the outer layers of the skin. They thus find utility as skin emollients, skin lubricants and sebum replacement agents. They are also used as fragrance fixatives and carriers for lipid soluble drugs. Examples of such drugs are vitamins such as A, D, and E, and keratolytic agents such as retinoic acid. In addition to these properties, squalane and squalene are further characterized by low freezing points, extending their utility to situations where other candidates cannot be used.

Squalene is a naturally occurring substance found in large quantities in shark liver oil and in smaller amounts (0.1-0.7%) in olive oil, wheat germ oil, rice bran oil and yeast. Its chemical name is 2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaene, and it has the structural formula:



Squalane is fully hydrogenated squalene, or 2,6,10,15,19,23-hexamethyltetracosane, with the structural formula:



There are certain disadvantages to the use of these compounds. Squalene absorbs oxygen, and upon doing so becomes highly viscous. It is also prone to oxidation and the resulting development of a rancid odor. Squalane is somewhat more stable but not completely. Neither are water-soluble and hence dispersible in an aqueous system, and both have an inherently oily character, leaving a residue on the skin with an unpleasant feel.

### SUMMARY OF THE INVENTION

#### 2.1 Topical Formulations for the Promotion of Hair Growth

A novel formulation for topically delivering active ingredients useful for promoting hair growth has now been developed with significant advantages over preexisting formulations. In accordance with the present invention, porous particles of an inert solid material contain the active ingredient, alone or in solution, retained inside the pores of the particles by capillary forces. The pores are interconnected and open to the

particle surface, permitting full diffusion outward of the retained active ingredients. The particles, which are preferably and most conveniently in the form of microspheres, are used either alone as a powder or as a dispersion in a suitable vehicle in a form resembling those of conventional skin preparations such as liniments, gels, lotions or ointments.

5

## 2.2 Topical Compositions used in the Treatment of Acne

A novel formulation for topically delivering active ingredients used in the treatment of acne has now  
10 been developed with significant advantages over preexisting formulations. In accordance with the present invention, porous particles of an inert solid material contain benzoyl peroxide and/or salicylic acid, alone or in solution, retained inside the pores of the particles by capillary forces. The pores are interconnected and open to the particle surface, permitting full diffusion outward of the retained active ingredients. The particles, which are preferably and most conveniently in the form of microspheres, are used either alone as  
15 a powder or as a dispersion in a suitable vehicle in a form resembling those of conventional skin preparations such as liniments, gels, lotions or ointments.

## 2.3 Fragrance Compositions

20

The present invention provides for fragrance compositions which comprise a fragrant substance incorporated in a polymeric delivery system. The fragrant substances are released slowly from the polymeric delivery system over time, prolonging the presence of the fragrance in the product in which it has been incorporated. Such controlled release also reduces the initial high concentration of fragrance normally  
25 associated with the use of a pure fragrance substance. Other advantages include improved compatibility of the fragrance compositions with a wide variety of products, regardless of product pH, ionic affinity, chemical composition, and the like. Surprisingly, it has been found that incorporation of a fragrance substance into the polymeric delivery system of the present invention does not substantially alter the olfactory characteristics of the fragrance. It might have been expected that the most volatile components of the fragrance would have been released from the delivery system initially, causing a change in the characteristics of the  
30 fragrance over time. Such undesirable effect has not been observed.

Fragrance compositions of the present invention are a dry, free-flowing product which will normally be incorporated in a carrier or other product. The composition, however, may be used alone by application directly on the skin.

35 According to the present invention, fragrance substances are incorporated in a polymer delivery system to form a novel fragrance composition having the advantages just discussed. The polymer delivery system comprises crosslinked polymer beads characterized by porous networks capable of retaining large amounts of the fragrance substance. The beads are noncollapsible, small diameter beads having relatively large pores and a relatively high ratio of pore volume to bead volume.

40 The fragrance compositions may be formed by suspension polymerization of suitable monomers in an immiscible phase including a porogen. Generally, the monomers and the porogen are first mixed together and the resulting mixture then suspended in the immiscible phase, usually an aqueous phase. The immiscible phase is then agitated to form droplets of the monomer mixture, and polymerization of the monomer mixture is initiated to form the desired beads.

45 Conveniently, the fragrance substance may be used as the porogen in a one-step process where there will be no substantial degradation of the substance under the conditions of polymerization. Alternatively, for more labile fragrance substances (particularly those which are heat or radiation labile), the polymeric beads may be preformed using a substitute porogen, usually an alkane, cycloalkane, or aromatic solvent. The beads are formed by suspension polymerization as described above, and the substitute porogen is  
50 extracted from the resulting bead product. The desired fragrance substance may then be introduced into the beads, typically by contact absorption, to create the desired final product. In addition to allowing the incorporation of labile UV absorptive substances, such a two-step preparation process allows greater control over the structure of the bead based on a wider choice of porogen substances and reaction conditions, and thus may be the desired preparatory method even for less labile substances.

55

#### 2.4 Vitamins and Vitamin Derivatives

A novel formulation for topically delivering vitamins, vitamin derivatives and vitamin-containing substances has now been developed with significant advantages over preexisting formulations. In accordance with the present invention, porous particles of an inert solid material contain vitamins, vitamin derivatives and vitamin-containing substances, alone or in solution, retained inside the pores of the particles by capillary forces. The pores are interconnected and open to the particle surface, permitting full diffusion outward of the retained active ingredients. The particles, which are preferably and most conveniently in the form of microspheres, are used either alone as a powder or as a dispersion in a suitable vehicle in a form resembling those of conventional skin preparations such as liniments, gels, lotions or ointments.

More specifically, the delivery systems of this invention constitute pre-formed, discrete, minute, high-capacity, hydrophobic, macroporous or macroreticular crosslinked, monionogenic polymer beads into whose macropores there have been incorporated vitamins such as vitamins A, D or E, derivatives thereof, such as vitamin E acetate, vitamin E palmitate, vitamin E linoleate, and vitamin-containing substances such as cod liver oil, and the like, as such or dissolved in a suitable organic solvent, alone or together with other formulating materials.

In the case of retinoids, porous particles of an inert solid material contain one or more retinoids, alone or in solution, retained inside the pores of the particles by the pore structure if solid and by capillary forces if liquid. The pores are interconnected and open to the particle surface, permitting full diffusion outward of the retained retinoids. The particles, which are preferably and most conveniently in the form of microspheres, are used either alone as a powder or as a dispersion in a suitable vehicle in a form resembling those of conventional skin preparations such as liniments, gels, lotions or ointments.

#### 2.5 Counterirritants

A novel formulation of counterirritants has now been developed with significant advantages over preexisting formulations. In accordance with the present invention, porous particles of an inert solid material contain counterirritants in liquid form, retained inside the pores of the particles by capillary forces. The pores are interconnected and open to the particles surface, permitting full diffusion outward of the retained counterirritants. The particles, which are preferably and most conveniently in the form of microspheres, are used either alone as a powder or as a dispersion in a suitable vehicle in a form resembling those of conventional skin preparations such as liniments, gels, lotions or ointments.

The retained counterirritant may either be in liquid or solid form, the liquids including those counterirritants which are liquid at ambient conditions as well as solid species dissolved in suitable solvents. These liquids diffuse out of the pores into either the vehicle if one is used or the natural bodily secretions present on one's skin at the applied area, in accordance with known principles of the diffusion of one liquid through another. Counterirritants in solid form are delivered to the applied area by gradually dissolving into either the vehicle or the bodily secretions at the points of exposure through the pore openings at the particle surfaces. Once dissolved, the counterirritants diffuse in the same manner as those which are normally liquid.

The volume of counterirritant retained in the pores awaiting diffusion is held in reserve with minimal exposure to the atmosphere. For those counterirritants which are volatile and produce irritating vapors, this retention in the pores reduces the rate of volatilization. At the same time, the amounts held in reserve are held out of contact with the skin until their release, thus lessening any high initial effect and preventing undesirable skin reactions to high concentrations.

#### 2.6 Epidermal Lipid Replacement Substances

A novel formulation for squalane and squalene has now been developed which overcomes these disadvantages. In accordance with the present invention, porous particles of an inert solid material contain one or both of the oils, alone or in solution, retained inside the pores of the particles by capillary forces. The pores are interconnected and open to the particle surface, permitting full diffusion outward of the retained oils. The particles, which are preferably and most conveniently in the form of microspheres, are used either alone as a powder or as a dispersion in a suitable vehicle in a form resembling those of conventional skin preparations such as liniments, gels, lotions or ointments.

In general, the active ingredients of various types described above diffuse out of the pores into either



the vehicle if one is used or the natural bodily secretions present on one's skin at the applied area, in accordance with known principles of the diffusion of one liquid through another.

The particles function as controlled delivery systems for the active ingredients, providing a wide range of advantages over the conventional formulations. Release of the active ingredients from the pores of the beads occurs in sustained manner, providing a continuous fresh supply of active substance to the epidermal area to which the preparation has been applied. Until it is released, the active ingredient is essentially unexposed to the atmosphere, and hence contact with oxygen and the risks of oxidation and decomposition are minimal. The formulation remains stable and active for a longer period of time, enhancing its shelf life. In addition, the particles have a dry, smooth, comfortable feel to the skin.

The activity-time curve of the active ingredient is thus extended and flattened out. The magnitude of the release rate is controlled by the pore volume distribution in the microsphere itself, notably the total pore volume and the average pore diameter. Selection of the values of these parameters according to predetermined standards provides control of the release rate to desired levels. This controlled release rate enhances the continuing treatment of the epidermal area, as sebum is continually produced by the skin. This also reduces the number of times that the skin formulation must be reapplied to the affected area.

The preparations remain active for a longer period of time after having been applied to the skin than conventional formulations, due to the sustained release character. The rate of release can be accelerated at any time thereafter by manual friction to stimulate the outward diffusion of the active ingredient. Thus, deeply retained materials may be brought to the surface and made available for their activity at will, many hours after the application of the formulation, without the need for a repeat application.

A further advantage is the ability of the formulation to withstand a higher concentration of active ingredient both inside the pores themselves and in the total preparation without the magnitude of side effects previously experienced at these levels.

As will be seen from the description which follows, the present invention is applicable to a wide range of active ingredients, and the degree of control which the system imparts to the various properties of the formulation and its use provide improved formulations of the active ingredients with a wide range of utility with enhanced safety and effectiveness.

### DETAILED DESCRIPTION OF THE SPECIFIC EMBODIMENTS

The beads or microspheres used in connection with the present invention are rigid, open-pore, chemically and biologically inert particles with the impregnant held inside the pores by capillary forces. The pores are interconnected and open to the particle surface to an extent that substantially full communication is provided between the internal pore space and the exterior of the particle.

In their most convenient form, the particles are generally spherical in shape, due to the use of suspension polymerization as a preferred method of preparation. While the microspheres may vary widely in size, those falling within the range of about one to about 100 microns in diameter, preferably from about 10 to about 40 microns, will provide the best results. Microspheres within these size ranges are appealing from an aesthetic point of view by imparting a smooth feel to the touch.

The pore dimensions within the spheres may also vary widely, with optimum dimensions depending on the chemical characteristics of the polymers used as well as the diffusive characteristics of the impregnant. Different systems will thus call for different optimum ranges of pore volume distribution to obtain the most desirable properties for the overall formulation. In general, however, best results are obtained with total pore volumes ranging from about 0.01 to about 4.0 cc/g, preferably from about 0.1 to about 2.0; surface areas ranging from about 1 to about 500 m<sup>2</sup>/g, preferably from about 20 to about 200; and average pore diameters ranging from about 0.001 to about 3.0 micron, preferably from about 0.003 to about 1.0 micron. Following conventional methods of measuring and expressing pore sizes, the pore diameters are calculated from the measurement of the surface area by B.E.T. nitrogen multipoint analysis and from the measurement of the pore volumes by the mercury intrusion method. The calculation is one commonly done by those skilled in the art.

The microspheres are conveniently formed by suspension polymerization in a liquid-liquid system. In general, a solution containing monomers, a polymerization catalyst (if used), and an inert but fully miscible liquid is formed which is immiscible with water. The solution is then suspended in an aqueous solution, which generally contains additives such as surfactants and dispersants to promote the suspension. Once the suspension is established with discrete droplets of the desired size, polymerization is effected (typically by activating the reactants by either increased temperature or irradiation). Once polymerization is complete,

the resulting rigid beads are recovered from the suspension. The beads at this point are solid porous structures, the polymer having formed around the inert, water-immiscible liquid, thereby forming the pore network. The liquid has accordingly served as a porogen, or pore-forming agent, and occupies the pores of the formed beads.

5 Certain impregnants may serve as the porogen, in which case the porous beads recovered from the suspension immediately after polymerization are substantially ready for use, following removal of surface moisture, and any further processing steps of this nature. In these cases, microsphere formation and incorporation of the impregnant is performed in a single step. This may accordingly be termed a one-step procedure. Those impregnants which are capable of serving as porogens will be liquid impregnants meeting  
10 the following criteria:

1. They are either fully miscible with the monomer mixture or capable of being made fully miscible by the addition of a minor amount of non-water-miscible solvent;
2. They are immiscible with water, or at most only slightly soluble;
3. They are inert with respect to the monomers, and stable when in contact with any polymerization  
15 catalyst used and when subjected to any conditions needed to induce polymerization (such as temperature and radiation); and
4. They are normally liquids or have melting points below the polymerization temperature. Solids can frequently be converted to liquid form by being dissolved in a solvent or by forming eutectic mixtures.

When using this method, the steps must be performed under an inert atmosphere such as nitrogen. If a  
20 polymerization catalyst is used, it must be one which does not oxidize the impregnant, if the latter is susceptible to oxidation. Azo catalysts are examples of such catalysts. Also, polymerization temperatures are best held within a moderate range.

As an alternative to the one-step procedure, the impregnant may be placed inside the pores of pre-formed dry porous polymer beads. The product is thus prepared in two steps performed in sequence, the  
25 polymerization being performed first with a substitute porogen which is then removed and replaced by the squalane or squalene. Materials suitable as substitute porogens will be substances which meet the same four criteria listed above for porogen impregnants.

This covers a wide range of substances. Preferred among these are hydrocarbons, particularly inert, nonpolar organic solvents. Some of the most convenient examples are alkanes, cycloalkanes, and ar-  
30 omatics. Examples of such solvents are alkanes of 5 to 12 carbon atoms, straight or branched chain, cycloalkanes of 5 to 8 carbon atoms, benzene, and alkyl-substituted benzenes such as toluene and the xylenes. Removal of the porogen may then be effected by solvent extraction, evaporation, or similar conventional operations.

A further advantage of the use of this two-step process is that it permits the removal of unwanted  
35 species from the polymerized structures prior to incorporation of the impregnant. Examples of unwanted species include unreacted monomers, residual catalyst, and surface active agents and/or dispersants remaining on the sphere surfaces. A further advantage of this technique is that it permits one to select the amount and type of porogen as a means of controlling the pore characteristics of the finished bead. One is thus no longer bound by the limitations of the impregnant as it affects the structure of the bead itself. This  
40 permits partial rather than full filling of the pores with the oil, and further control over pore size and distribution by selection among swelling and non-swelling porogens.

Extraction of the porogen and its replacement with (i.e., impregnation of the dry bead with) the impregnant in the two-step procedure may be effected in a variety of ways, depending on the chemical  
45 nature of the porogen and its behavior in combination with that of the other species present. The beads are first recovered from the suspension by filtration, preferably using vacuum filtration apparatus (such as a Buchner funnel). The beads are then washed with an appropriate solvent to remove organic species not bound to the polymer, including surfactants having deposited on the bead surfaces from the aqueous phase, unreacted monomers and residual catalysts, and the porogen itself. An example of such a solvent is isopropanol, either alone or in aqueous solution. Once washing is complete, the solvent itself is removed by  
50 drying, preferably in a vacuum.

In certain cases, an alternative method of extraction may be used, i.e., where the porogen, unreacted monomer and water will form an azeotrope. In these cases, steam distillation is an effective way of extracting porogen from the beads. This again may be followed by drying under vacuum.

Once the beads are rendered dry and free of the substitute porogen and any unwanted organic  
55 materials, they are impregnated with the impregnant according to conventional techniques. The most convenient such technique is contact absorption. Solid active ingredients are first dissolved in a solvent, and the resulting solution is absorbed by the beads. The solvent may either be retained in the finished product or removed by conventional means such as evaporation or extraction using a further solvent. For those solid

Ingredients having limited solubility in a particular solvent. high contents in the finished bead can be attained by repeated absorptions each followed by solvent removal.

The polymerization process and the various parameters and process conditions involved in the polymerization can be selected and adjusted as a means of controlling the pore characteristics and consequently the capacity and release characteristics of the ultimate product. For example, proper selection of the crosslinking means, the amount and type of crosslinking agent, and the amount and type of porogen are means of attaining such control. Certain polymerization conditions may also be varied to such effect, including temperature, degree of radiation where used, degree of agitation and any other factors affecting the rate of the polymerization reaction.

Crosslinking in the polymer formation is a major means of pore size control. Monomers which may be polymerized to produce crosslinked polymer beads in accordance with the present invention include polyethylenically unsaturated monomers, i.e., those having at least two sites of unsaturation, and monoethylenically unsaturated monomers in combination with one or more polyethylenically unsaturated monomers. In the latter case, the percentage of crosslinking may be controlled by balancing the relative amounts of monoethylenically unsaturated monomer and polyethylenically unsaturated monomer. The polymer beads of the present invention will have greater than 10% crosslinking, preferably from about 10% to about 80% crosslinking, and most preferably from about 20% to about 60% crosslinking. The percentage crosslinking is defined among those skilled in the art as the weight of polyethylenically unsaturated monomer or monomers divided by the total weight of monomer, including both polyethylenically unsaturated and monoethylenically unsaturated monomers.

Monoethylenically unsaturated monomers suitable for preparing polymer beads for the polymer delivery system include ethylene, propylene, isobutylene, diisobutylene, styrene, ethylvinylbenzene, vinylpyridine, vinyltoluene, and dicyclopentadiene; esters of acrylic and methacrylic acid, including the methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, amyl, hexyl, octyl, ethylhexyl, decyl, dodecyl, cyclohexyl, isobornyl, phenyl, benzyl, alkylphenyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, propoxymethyl, propoxyethyl, propoxypropyl, ethoxyphenyl, ethoxybenzyl, and ethoxycyclohexyl esters; vinyl esters, including vinyl acetate, vinyl propionate, vinyl butyrate and vinyl laurate; vinyl ketones, including vinyl methyl ketone, vinyl ethyl ketone, vinyl isopropyl ketone, and methyl isopropenyl ketone; vinyl ethers, including vinyl methyl ether, vinyl ethyl ether, vinyl propyl ether, and vinyl isobutyl ether; and the like.

Polyethylenically unsaturated monomers which ordinarily act as though they have only one unsaturated group, such as isopropene, butadiene and chloroprene, may be used as part of the monoethylenically unsaturated monomer content.

Polyethylenically unsaturated crosslinking monomers suitable for preparing such polymer beads include diallyl phthalate, ethylene glycol diacrylate, ethylene glycol dimethacrylate, trimethylolpropanetrimethacrylate, divinylsulfone; polyvinyl and polyallyl ethers of ethylene glycol, of glycerol, of pentaerythritol, of diethyleneglycol, of monothio- and dithio-derivatives of glycols, and of resorcinol; divinylketone, divinylsulfide, allyl acrylate, diallyl maleate, diallyl fumarate, diallyl succinate, diallyl carbonate, diallyl malonate, diallyl oxalate, diallyl adipate, diallyl sebacate, divinyl sebacate, diallyl tartrate, diallyl silicate, triallyl tricarballoylate, triallyl aconitate, triallyl citrate, triallyl phosphate, divinyl naphthalene, divinylbenzene, trivinylbenzene; alkyldivinylbenzenes having from 1 to 4 alkyl groups of 1 to 2 carbon atoms substituted on the benzene nucleus; alkyltrivinylbenzenes having 1 to 3 alkyl groups of 1 to 2 carbon atoms substituted on the benzene nucleus; trivinylanthracenes, and polyvinylanthracenes.

The preferred polymer bead of the present invention will be free from reactive groups which will interact with the porogen and the active ingredient which is ultimately incorporated in the composition. In particular, the beads should be free from reactive amino, hydroxyl, carboxylic, and other reactive functionalities. Such beads will not readily undergo unwanted reactions, will be stable over a wide pH range, will resist moderate oxidation and reduction, will be stable at higher temperatures, will resist attack by moisture, and will have a relatively long shelf life.

Particularly preferred polymer delivery systems of the present invention are formed by the copolymerization of styrene and divinylbenzene, vinyl stearate and divinylbenzene, 4-vinylpyridine and ethylene glycol dimethacrylate, or methylmethacrylate and ethylene glycol dimethacrylate. Usually, the monoethylenically unsaturated monomer will be present at from about 20% to 80% of the monomer mixture, with the polyethylenically unsaturated monomer forming the remainder of the mixture. Particularly preferred is the styrene-divinylbenzene polymeric bead which consists essentially of a hydrocarbon backbone with benzene rings and which is substantially completely free from reactive groups.

Once the microspheres are formed and dried, they are impregnated with the impregnant by contact absorption. As an option, the impregnant may be used in the form of a solution in a suitable organic solvent for purposes of decreasing viscosity and facilitating absorption. Examples of such solvents are liquid

petrolatum, ether, petroleum ether, alcohols including methanol, ethanol and higher alcohols, aromatics including benzene and toluene, alkanes including pentane, hexane and heptane, ketones including acetone and methyl ethyl ketone, chlorinated hydrocarbons including chloroform, carbon tetrachloride, methylene chloride and ethylene dichloride, acetates including ethyl acetate, and oils including isopropyl myristate, diisopropyl adipate and mineral oil. After absorption of the solution, the solvent can be evaporated or, if desired, retained inside the pores together with the impregnant. Other formulating materials, such as carriers or adjuvants such as fragrances, preservatives, antioxidants, and other emollients can also be present, and will be incorporated into and onto the beads together with the impregnants and any other materials present.

The impregnant, whether it be pure active ingredient, a mixture of active ingredients or a solution of active ingredient, will generally comprise between approximately 5% and approximately 65% of the total weight of the impregnated beads. When the active ingredient is a potent drug, it will generally be in the form of a dilute solution, and the weight percent of the active ingredient itself will range as low as 0.01% based on the total weight of the impregnated beads.

For topical application, the impregnated beads of the present invention may be used alone or in the form of fluid compositions or preparations similar to those commonly used for skin treatment, for example: gels, creams, lotions, ointments, sprays, powders, or oils. Appropriate vehicles for particular areas or methods of application will be readily apparent to those skilled in the art. When liquid vehicles are used (such as gels, creams, lotions, ointments or oils) and the impregnant is a solution of an active ingredient in a solvent, the solvent and vehicle must be immiscible so that outward diffusion of the active ingredient will not be accelerated by mutual diffusion between the solvent and vehicle. Appropriate combinations will therefore include the combination of a polar solvent and a nonpolar vehicle, and the combination of a nonpolar solvent and a polar vehicle.

The following are some of the considerations specific to various particular types of impregnants, plus examples of preparation and utility. The examples are offered solely for purposes of illustration, and are intended neither to limit nor define the invention in any manner. All parts and percentages are by weight, unless otherwise stated.

### 3.1 Topical Formulations for the Promotion of Hair Growth

For topical application, the impregnated beads of the present invention may be used alone or in the form of fluid compositions or preparations similar to those commonly used for skin treatment, for example: gels, creams, lotions, ointments, sprays, powders, or oils. Appropriate vehicles for particular impregnants or areas or methods of application will be readily apparent to those skilled in the art.

Minoxidil, the preferred hair growth promotion agent, is a solid soluble in propylene glycol, and may only be incorporated into the beads by the two-step process.

#### 3.1.1 Example

A 2000 ml four-necked reaction flask equipped with a motorized stirrer, reflux condenser, thermometer, and nitrogen inlet were evacuated and purged with nitrogen. 800 parts of deionized water, 6.4 parts of gum arabic and 6.4 parts of a lignosulfonate available from Reed Lignins, Inc., under the trademark Marasperse N-22, were charged to the reaction flask. The mixture was stirred for about 30 minutes at about 50 °C until the dispersants (gum arabic and lignosulfate) dissolved to form an aqueous phase.

To this mixture was added a freshly prepared solution of 85.6 parts of styrene (99.8% purity), 102.3 parts of commercial divinylbenzene (55.6% divinyl benzene, 42.3% ethylvinylbenzene), 5.3 parts of benzoyl peroxide (70% active ingredient and 30% water), and 187.9 parts of toluene to serve as a porogen. The aqueous phase and organic solution were agitated by stirring at a rate adjusted to give a plurality of droplets having an average droplet diameter of about 10-60 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400X) with the droplets being stabilized by the dispersants. This rate was approximately 1200 rpm. The reaction mixture was heated to about 78 °C and constantly stirred while a slow stream of nitrogen is passed through the reaction vessel, thus forming porous beads of crosslinked styrene/divinylbenzene copolymer having heptane entrapped within the network of pores. The mixture was stirred another 22 hours at 78 °C and allowed to cool to room temperature. The mixture was then diluted with 200 parts of water, and the porous polymeric beads were removed from the reaction flask by filtration. The filtered beads were washed initially three times with one

liter portions of deionized water to remove the dispersants, followed by several washes of isopropanol/acetone mixture (7:3, respectively, by weight) to remove any residual, unreacted monomer and the heptane used as the porogen during polymerization. The beads were filtered and then dried at 65°C in vacuo.

5 The calculated or theoretical crosslinking density of the purified beads was 30%. This density is calculated by multiplying the weight of divinylbenzene (102.3 g) by the purity of the divinylbenzene (.55) to get the actual weight of pure divinylbenzene which is then divided by the total weight of monomer (102.3 g + 85.6 g).

The surface area of a sample of the purified beads was determined by the B.E.T. method to be 1.8  
10 meters<sup>2</sup>/gram. The B.E.T. method is described in detail in Brunauer, S. Emmet, P.H., and Teller, E., J. Am. Chem. Soc., 60, 309-16 (1938).

The particle size of the beads was determined by an optical microscope to be 60 microns or less with an average approximate particle size diameter of about 10 microns.

Minoxidil was obtained from Minoxidil 10 mg tablets (Upjohn, Loniten Tablet, 10 mg) by an ethanol  
15 extraction in which Minoxidil tablets were first ground into a powder. 3.4 grams of the ground powder were then mixed with 15 ml of ethanol (95% ethanol and 5% isopropyl alcohol) and the resultant mixture was stirred for 10 minutes. The mixed solution produced by stirring was then filtered and the ethanol was evaporated. 0.35 g of white Minoxidil solid, which shall be referred to as CH 215M, was obtained.

In a first example of preparation of polymeric beads having a solution of an active ingredient useful for  
20 promoting hair growth dissolved in a percutaneous absorption enhancer held within a network of pores of the polymeric beads, 10.6 mg of the white Minoxidil solid CH 215M was dissolved in 2 grams of a 50:50 solution of propylene carbonate/ethanol. 1.5 grams of the polymeric beads CH 215 was then mixed into the solution until the product is homogeneous. The Minoxidil content in the resulting product, which shall be referred to as CH 215 A-3, was 3 mg/g. In a second example, 1.2 parts of the white Minoxidil solid CH  
25 215M, was added to 32.1 parts of propylene glycol and stirred in a flask at 45°C until the white Minoxidil solid CH 215M was completely dissolved. Thereafter, 61.7 parts of polymeric beads (CH 215) were added to the solution which was mixed until the product is homogeneous. The Minoxidil content in the resulting product was 12 mg/g.

A composition useful in the method of the present invention is then prepared by adding 9.09 parts of  
30 CH 215 A-3 to 90.01 parts of a medium comprised of petroleum jelly. The product was then mixed until homogeneous. The Minoxidil content in the resulting product was 1.1 mg/g. This product could then be rubbed into portions of the skin and scalp to enhance hair growth.

While the above description has described the preparation of a composition useful in the method of the  
35 present invention to promote hair growth, it should be noted that a product containing higher concentrations of Minoxidil could be used to achieve the known cardiovascular effects of Minoxidil. Thus, for example, such a product could be rubbed onto the skin to provide a topical application of Minoxidil, as opposed to an oral dosage, for use in controlling hypertension.

### 40 3.2 Topical compositions used in the Treatment of Acne

Substances active as acne treatment agents which can be used in the present invention include benzoyl  
45 peroxide, salicylic acid and resorcinol. Benzoyl peroxide and salicylic acid are preferred. Benzoyl peroxide may not be used as a porogen, although salicylic acid may. In general, the two-step process is preferred for these substances.

#### 3.2.1 Example

50 A 2000 ml four-necked reaction flask equipped with a motorized stirrer, reflux condenser, thermometer, and nitrogen inlet was evacuated and purged with nitrogen. 800 parts of deionized water, 6.4 parts of gum arabic and 6.4 parts of a sodium-based lignosulfonate available from Reed Lignins, Inc., under the trademark Marasperse N-22, were charged to the reaction flask. The mixture was heated, with stirring, in an oil bath at about 50°C until the dispersants (gum arabic and lignosulfate) dissolved to form an aqueous  
55 phase.

To this mixture there was then added a freshly prepared solution of 102.3 parts of styrene (99.8% purity), 85.6 parts of commercial divinylbenzene (55.6% divinyl benzene, 42.3% ethylvinylbenzene), 5.3 parts of benzoyl peroxide (70% active ingredient and 30% water), and 130 parts of heptane. The aqueous

phase and organic solution were agitated by stirring at a rate adjusted to give a plurality of droplets having an average droplet diameter of about 10-60 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400X) with the droplets being stabilized by the dispersants. This rate is approximately 1200 rpm. The reaction mixture was then heated to about 80 °C and maintained at that temperature for about 20 hours, at the previously adjusted stirring rate, to form porous beads of crosslinked styrene/divinylbenzene copolymer having heptane entrapped within the network of pores. The mixture was then cooled, diluted with 200 parts of water, and the porous polymeric beads were removed from the reaction flask by filtration. The filtered beads were washed initially three times with one liter portions of deionized water to remove the dispersants, followed by three washes with 0.6 liter portions of isopropanol: acetone mixture (7:3, respectively, by weight) to remove any residual, unreacted monomer and the heptane used as the porogen during polymerization. The beads were then dried in an oven at 80-100 °C for eight hours.

The average particle diameter of these beads was 25 microns, as measured by a Sedimentation Micromeritics Microsizer-5300, an instrument available from Micromeritics Instrument Company, Norcross, Georgia. The particle diameter determination method is described in detail in the "Microsizer 5300 Particle Size Analyzer Instruction Manual" (1984) associated with the instrument.

The calculated or theoretical crosslinking density of the purified beads is 25%. This density is calculated by multiplying the weight of divinylbenzene (85.6 parts) by the purity of the divinylbenzene (55.6%) to get the actual weight of pure divinylbenzene which is then divided by the total weight of monomer (85.6 parts + 102.3 parts) and multiplied by 100.

The surface area of a sample of the purified beads was determined by the B.E.T. nitrogen multipoint analysis to be 91.2 m<sup>2</sup>/g while the pore volume was determined by the mercury intrusion method to be 1.0 cc/g. The B.E.T. method is described in detail in Brunauer, S., Emmet, P.H., and Teller, E., J. Am. Chem. Soc., 60, 309-16 (1938). The mercury intrusion method is described in detail in "Advanced Experimental Techniques in Powder Metallurgy," pages 225-252, (Plenum Press, 1970).

### 3.2.2 and 3.2.3 Examples

By repeating the procedure of Example 3.2.1 in every essential detail, except for the weights of monomers and porogen employed, porous crosslinked polymer beads were obtained having the following characteristics listed in Table 3.2.1:

TABLE 3.2.1

Example	Ratio Of Parts Styrene/DivinylBenzene/Porogen	Calculated Crosslinking Density, %	Avg. Particle Diam, $\mu$ m	Surface Area m <sup>2</sup> /g	Pore Volume ml/g
2	89/100/180 (porogen = mineral oil)	29	25	75	1.36
3	85.6/102.3/188 (porogen = toluene)	30	25	1.8	0.04

### 3.2.4 Example

A 10 part portion of the macroporous crosslinked polymer beads prepared as described in each of Examples 3.2.1-3.2.3 above was mixed at room temperature with 16 parts of a 12.5% solution of benzoyl peroxide in acetone, and the resulting suspensions were hand-stirred for a few minutes. The thus-obtained homogeneous wet powders were washed three times with 30 ml portions of deionized water in a funnel, then air dried at room temperature for 20 hours. The benzoyl peroxide contents entrapped within these beads' macropores as determined by titration with iodine in isopropanol and based on the total weight of beads and entrapped benzoyl peroxide, were as follows:

TABLE 3.2.2

Beads Of Example	Wt Of Water, %	Wt. Of Benzoyl Peroxide, %
1	1	12.2
2	1	12.1
3	8	9.6

### 3.2.6 Example

Two 10 part portions of the macroporous crosslinked polymer beads prepared as described in Example 3.2.1 above were mixed at room temperature with a 14 part portion of a 12.5% solution of benzoyl peroxide in acetone and a 10 part portion of a 20% solution of salicylic acid in acetone, respectively. The resulting wet poders were hand-stirred until homogeneous, then air-dried at room temperature for 20 hours. Their respective contents of benzoyl peroxide and salicylic acid, as determined by titration with iodine and dilute aqueous sodium hydroxide, respectively, and based on the total weight of beads and entrapped benzoyl peroxide and salicylic acid, were:

Benzoyl peroxide 11.3%

Salicylic acid 16%

The two lots of beads were then commingled to provide a therapeutic delivery system for topically applying benzoyl peroxide and salicylic acid together to the skin.

### 3.3 Fragrance Compositions

Fragrant substances useful in the fragrance compositions of the present invention include the following general classes:

	Class	Examples
5	(1) Flower oils obtained from cultivated flowers, usually by steam distillation or solvent extraction.	Rose, lilac, jasmine, apple blossoms, lavender, carnation, wisteria, and ylang.
10	(2) Essential oils obtained from plant parts, such as roots, barks, leaves, fruits, and the like, usually by steam distillation.	Sandalwood, vetiver, oakmoss, bergamot, rosewood, patchouli, orris, citrus oils, and citronella, sage, fern, and spice.
15	(3) Substance of animal origin.	Musk, ambergris, civet, castoreum, etc.
20	(4) Chemical compounds isolated from naturally-occurring substances.	Geraniol and citronellol
25	(5) Synthetic substances, including substances mimicking natural substances and compounds, and substances which are not related to natural substances.	Phenyl ethyl alcohol, methyl benzoate, benzaldehyde, benzyl salicylate, musk ambrette, ethyl acetate, and ethyl brassylate.
30	(6) Resinoids	
35		Styrax, benzoin, myrrh, olibanum, opoponax, and galbanum.
40		

45 The fragrant substances may be used individually or, more typically, will be combined to achieve a desired aroma prior to incorporation in the fragrance compositions of the present invention. The fragrant substances may also be dissolved in a suitable liquid, such as an alcohol, ester, or other organic solvent, or used without dilution, depending on the physical characteristics of the fragrance and desired strength of the fragrant composition. Many of the oils will be suitable for use as the porogen without dilution, while it will often be desirable to dissolve the fragrant substance if it is desired to attenuate the aroma.

50 Once the fragrance compositions have been prepared, by either the one-step or two-step procedures described above, it may be used alone or further incorporated in a carrier or vehicle or in virtually any type of product where it is desired to impart an aroma. The composition may be used alone as a perfume by simply applying the composition, which is a dry powder, to the skin. The composition may also be incorporated in a suitable carrier or vehicle, typically an alcohol, and used as a perfume.

55 More commonly, the fragrance compositions of the present invention will be incorporated in other products in order to impart a fragrance. For example, the composition is ideally suited for combining with other powders, such as body powders, foot powder, and the like, by simple mixing. The fragrant compositions may also be incorporated into a wide variety of other products, such as soaps, detergents, paper goods, and the like, by introducing the composition at the appropriate point in the fabrication



procedure.

### 3.3.1 Example

5 A 2000 ml four-necked reaction flask equipped with a motorized stirrer, reflux condenser, thermometer, and nitrogen inlet was evacuated and purged with nitrogen. 800 part of deionized water, 6.4 parts of gum arabic and 6.4 parts of sodium-based lignosulfonate (Reed lignin) available from the American Can Co. under the trademark Marasperse N-22, were charged to the reaction flask. The mixture was heated, with  
10 stirring, in an oil bath at about 50 °C until the dispersants (gum arabic and lignosulfate) dissolved to form an aqueous phase.

To this mixture there was then added a freshly prepared solution of 85.6 parts of styrene (99.8% purity), 102.3 parts of commercial divinylbenzene (55.6% divinyl benzene, 42.3% ethylvinylbenzene), 5.3 parts of benzoyl peroxide (70% active ingredient and 30% water), and 188 parts of toluene (porogen). The  
15 aqueous phase and organic solution were agitated by stirring at a rate adjusted to give a plurality of droplets having an average droplet diameter of below about 60 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400X) with the droplets being stabilized by the dispersants. This rate was approximately 1000 rpm. The reaction mixture was then heated to about 78 °C and maintained at that temperature for about 20 hours, at the previously adjusted stirring rate, to form  
20 porous beads of crosslinked styrene/divinylbenzene copolymer having toluene entrapped within the network of pores. The mixture was then cooled, diluted with 1000 parts of water, and the porous polymeric beads removed from the reaction flask by filtration. The filtered beads were washed initially three times with one liter portions of water to remove the dispersants, followed by three washes with one liter portions of acetone to remove any residual, unreacted monomer and the toluene used as the porogen during polymerization.  
25 The beads were then dried in an oven at 70 °C for 10 hours. These beads were white and opaque in appearance, indicating the microporosity, and had an average particle diameter of less than 50 microns. They had a pore volume of 0.04 ml/g as measured by a mercury intrusion porosimeter.

The calculated or theoretical crosslinking density of the purified beads was 30%. This density was calculated by multiplying the weight of divinylbenzene (102.3 parts) by the purity of the divinylbenzene  
30 (0.556) to get the actual weight of pure divinylbenzene which was then divided by the total weight of monomer (85.6 parts + 102.3 parts) and multiplied by 100.

The surface area of a sample of the purified beads was determined by the B.E.T. method to be 1.8 meters<sup>2</sup>/gram while the pore volume was determined by the mercury intrusion method to be 0.04 ml/gram. The B.E.T. method is described in detail in Brunauer, S. Emmet, P.H., and Teller, E., *J. Am. Chem. Soc.*,  
35 60:309-16 (1938). The mercury intrusion method is described in detail in "Advanced Experimental Techniques in Powder Metallurgy", pages 225-252 (Plenum Press, 1970).

### 3.3.2 Example

40 A two-liter four-necked reaction flask equipped as described in Example 3.3.1 was evacuated and purged with nitrogen. An aqueous phase made up of 800 parts of deionized water, 8 parts of gum arabic and 8 parts of Marasperse N-22 was added to the flask, and an organic solution made up of 100 parts of methyl methacrylate, 100 parts of ethylene glycol dimethacrylate, 10 parts of butyl methacrylate, 2 parts of  
45 lauroyl peroxide and 173 parts of toluene was dispersed in the aqueous phase with strong agitation (stirrer speed approximately 1000 rpm) to obtain a plurality of droplets having an average droplet diameter of below about 50 microns, as determined by visual observation of a sample of the droplets being stabilized by the dispersants.

The reaction mixture was then heated to 80 °C and maintained at that temperature for 8 hours while  
50 maintaining a nitrogen flow of 1 ml/minute, to form porous beads of crosslinked methyl methacrylate/butyl methacrylate/ethylene glycol dimethacrylate terpolymer having toluene entrapped within the pores. The reaction mixture was then cooled and the beads were collected by filtration, washed three times with 1000 parts of water, and three times with 1000 parts of isopropanol, and then dried in air at room temperature.

The calculated or theoretical crosslinking density of the purified beads was 47.6%, and was calculated  
55 by dividing the weight of ethylene glycol dimethacrylate (100 parts) by the total weight of monomer 210 parts + (100 parts + 110 parts) and then multiplying by 100.

The surface area of a sample of the purified beads was 52 meters<sup>2</sup>/gram and the pore volume was 0.4 ml/gram, determined as described in Example 1 above.

**3.3.3-3.3.6 Examples**

By repeating the procedure of Example 3.3.1 in every essential detail except for the weights of monomers employed and, in one case, the porogen used, the macroporous crosslinked polymer beads described in Table 3.3.1 below were obtained.

TABLE 3.3.1

Example	Methyl Methacrylate	Ethylene Glycol Dimethacrylate	Porogen Parts	Calculated Crosslinking Density	Average Particle Diameter, m	Surface Area m <sup>2</sup> /g	Pore Volume ml/g
3	100	100	173 <sup>1</sup>	50%	25	73.8	0.405
4	150	150	450 <sup>1</sup>	50%	15	95.8	0.508
5	100	100	200 <sup>1</sup>	50%	25	84.0	0.38
6	210	90	200 <sup>2</sup>	50%	15	2.34	0.58

<sup>1</sup> Toluene

<sup>2</sup> Heptane

**3.3.6 Example**

A 5 part portion of the macroporous crosslinked polymer beads prepared as described in each of Examples 3.3.1 and 3.3.2 above were hand mixed at room temperature with a 5 part portion of Christmas tree air freshener fragrance (H&R A670201). The fragrance content of the beads was determined to be 50%.

A 1 part sample of each batch of fragrance containing beads, together with a 0.5 part sample of unabsorbed fragrance absorbed on filter paper, were held in air at room temperature (about 25° C) and atmospheric pressure for 24 hours, during which time the percentage weight loss by weighing the bead and filter paper samples. The results of these weight loss determinations demonstrated that a high degree of sustained release over a longer period of time was achieved using the polymeric fragrance delivery systems of this invention.

**3.3.7 Example**

Six-part portions of the macroporous crosslinked polymer beads of Examples 3.3.5 and 3.3.6 are mixed with four parts of methyl benzoate fragrance. The fragrance content of the beads is calculated to be 40%.

**3.4 Vitamins and Vitamin Derivatives**

Any vitamin, vitamin derivative or vitamin-containing substance which can be applied topically to human or animal skin can be absorbed in the above-described minute polymer beads to form the novel, macroporous, high capacity topical delivery systems of this invention. The chemical nature of each species will establish whether or not it can be used in the oneDstep procedure. Retinoids, for example, will in general only be used in the twoDstep procedure. Vitamin E acetate and lineoleate, on the other hand, can be used in the oneDstep procedure.

**3.4.1 Example**

A 2000 ml four-necked reaction flask equipped with a motorized stirrer, reflux condenser, thermometer, and nitrogen inlet was evacuated and purged with nitrogen. 800 parts of deionized water, 6.4 parts of gum arabic and 6.4 parts of a sodium-based lignosulfonate available from Reed Lignins, Inc., under the trademark Marasperse N-22, were charged to the reaction flask. The mixture was heated, with stirring, in an

oil bath at about 50° C until the dispersants (gum arabic and lignosulfate) dissolved to form an aqueous phase.

To this mixture was then added a freshly prepared solution of 90.5 parts of styrene (99.8% purity), 55 parts of commercial divinylbenzene (55.6% divinyl benzene, 42.3% ethylvinylbenzene), 2 parts benzoyl peroxide (70% active ingredient and 30% water), and 69.4 parts of heptane (porogen). The aqueous phase and organic solution were agitated by stirring at a rate adjusted to give a plurality of droplets having an average droplet diameter of about 10-60 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400X) with the droplets being stabilized by the dispersants. This rate was approximately 1200 rpm. The reaction mixture was then heated to about 80° C and maintained at that temperature for about 12 hours, at the previously adjusted stirring rate, to form porous beads of crosslinked styrene/divinylbenzene copolymer having toluene entrapped within the network of pores. The mixture was then cooled and the porous polymeric beads are removed from the reaction flask by filtration. The filtered beads were washed initially three times with one liter portions of deionized water to remove the dispersants, followed by three washes with 0.6 liter portions of isopropanol to remove any residual, unreacted monomer and the toluene used as the porogen during polymerization. The beads were then dried in an oven at 80° C for eight hours.

The average particle diameter of these beads, which are white and opaque in appearance, indicating their macroporosity, was less than 35 microns, as measured by a mercury intrusion porosimeter or by optical microscopy.

The calculated or theoretical crosslinking density of the purified beads was 21.01%. This density was calculated by multiplying the weight of divinylbenzene (55 parts) by the purity of the divinylbenzene (0.556) to get the actual weight of pure divinylbenzene which was then divided by the total weight of monomer (90.5 parts + 55 parts) and multiplied by 100.

The surface area of a sample of the purified beads was determined by the B.E.T. method to be 36.41 meters<sup>2</sup>/gram while the pore volume was determined by nitrogen adsorption isotherm to be 0.206 ml/gram. The B.E.T. method is described in detail in Brunauer, S. Emmet, P.H., and Teller, E., J. Am. Chem. Soc., 60, 309-16 (1938). The nitrogen adsorption isotherm method is described in detail in Barrett, E.P., Joyner, L.G. and Helenda, P.P., J. Am. Chem. Soc., 73, 373-80 (1951).

#### 3.4.2 Example

The procedure of Example 3.4.1 was repeated in every essential detail, except for the following: 800 parts of deionized water were used to dissolve 5.6 parts of gum arabic and 5.6 parts of Marasperse N-22 at about 23° C; 105 parts of styrene and 9.5 parts of divinylbenzene were used; 2.8 parts of benzoyl peroxide (70% active ingredient and 30% water) and 120 parts of heptane were employed during polymerization and stirring was adjusted to give an average droplet diameter of below about 50 microns (rate approximately 800-1600 rpm); three 300 ml portions of isopropanol were used to wash the beads. The macroporous crosslinked polymer beads obtained had the following characteristics:

Calculated Crosslinking Density, %:	26.4
Average Particle Diameter, $\mu$ :	25
Surface Area, m <sup>2</sup> /g:	85.9
Pore Volume, ml/g:	0.44

#### 3.4.3 Example

A two liter four-necked reaction flask equipped as described in Example 3.4.1 was evacuated and purged with nitrogen. An aqueous phase made up of 600 parts of deionized water, 6.0 parts of gum arabic and 6.0 parts of Marasperse N-22 was added to the flask, and an organic solution made up of 72.0 parts of methyl methacrylate, 78.0 parts of ethylene glycol dimethacrylate, 2.0 parts of benzoyl peroxide (70% active ingredient and 30% water) and 108.4 parts of toluene was dispersed in the aqueous phase with strong agitation (stirrer speed approximately 1000 rpm) to obtain a plurality of droplets having an average droplet diameter of below about 50 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400 x), with the droplets being stabilized by the dispersants.

The reaction mixture was then heated to 80° C and maintained at that temperature for 12 hours while maintaining a nitrogen flow of 6 ml/minute, to form porous beads of crosslinked methyl

methacrylate/ethylene glycol dimethacrylate copolymer having toluene entrapped within the pores. The reaction mixture was then cooled and the beads were collected by filtration, washed three times with 1000 part portions of water, then three times with 1000 part portions of isopropanol, and then dried at 80 °C for about 8 hours.

5 The calculated or theoretical crosslinking density of the purified beads was 52%, and was calculated by dividing the weight of ethylene glycol dimethacrylate (78.0 parts) by the total weight of monomer (72.0 parts + 78.0 parts) and then multiplying by 100.

The surface area of a sample of the purified beads is 98 meters<sup>2</sup>/gram and the pore volume is 0.36 ml/gram, determined as described in Example 3.4.1 above.

10

#### 3.4.4 Example

The procedure of Example 3.4.3 was again repeated in every essential detail except for the following:  
 15 400 parts of deionized water were used to dissolve 4.0 parts of gum arabic and 4.0 parts of Marasperse N-22; 70 parts of methyl methacrylate and 30 parts of ethylene glycol dimethacrylate were used; 1.0 part of lauroyl peroxide and 69.4 parts of toluene were employed during polymerization; the reaction was conducted at 85 °C for 12 hours. The resulting polymer beads were collected and washed with three 1000 ml portions of deionized water followed by three 1000 ml portions of isopropanol, and then dried at 80 °C  
 20 for about 8 hours. The macroporous crosslinked polymer beads obtained had the following characteristics:

Calculated Crosslinking Density, %:	30
Average Particle Diameter, $\mu\text{m}$ :	30
Surface Area, M <sup>2</sup> /g:	12.54
25 Pore Volume, ml/g:	0.170

#### 3.4.5-3.4.7 Examples

30 By repeating the procedure of Example 3.4.4 in every essential detail except for the weights of monomers and solvents employed, the macroporous crosslinked polymer beads described in Table 3.4.1 below were obtained.

35

40

45

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TABLE 3.4.1

Example	Methyl Methacrylate, g	Ethylene Glycol Dimethacrylate, g	Porogen Toluene, g	Calculated Crosslinking Density, %	Average Particle Diameter, $\mu$ m	Surface Area $m^2/g$	Pore Volume, ml/g
5	20.0	80.0	85.6	80.0	30	301.93	0.553
6	40.0	60.0	69.4	60.0	25	95.07	0.388
7	80.0	20.0	86.7	20.0	40	0.72	0.044

**3.4.8 Example**

5 A 70 part portion of the macroporous crosslinked polymer beads prepared as described in Example 3.4.3 above was mixed at room temperature with 157 parts of isopropanol in a glass beaker with an agitator. 30 parts of vitamin E linoleate are added slowly, with stirring, and the resulting suspension is stirred for about five minutes. The solvent is then allowed to evaporate to dryness in a fume hood at room temperature for 2 days. The beads contain 30.0% vitamin E linoleate entrapped within their macropores.

**3.4.9 Example**

15 By repeating the procedure of Example 3.4.8 using 35 parts of the styrene divinylbenzene macroporous crosslinked polymer beads prepared as described in Example 3.4.2, 15 parts of vitamin E linoleate and 88.7 parts of Isopropanol as the solvent, beads containing 30% vitamin E linoleate entrapped within their macropores are obtained.

**3.4.10 Example**

20 By again repeating the procedure of Example 3.4.8 using 350 parts of the methyl methacrylate/ethylene glycol dimethacrylate macroporous crosslinked polymer beads prepared as described in Example 3.4.3, 160 parts of vitamin E linoleate and 200 parts of Isopropanol, beads containing 32% vitamin E linoleate  
25 entrapped within their macropores are obtained.

**3.4.11-3.4.16 Examples**

30 The procedure of Example 3.4.8 is repeated using the following vitamins, vitamin derivatives, vitamin-containing substances and solvents in the indicated amounts:

Active Ingredient, parts	Macroporous Polymer, parts	Solvent, parts
Vitamin A, 1.0	1.0	Ethanol, 4.0
Vitamin D, 30.0	30.0	Isopropanol, 39.0
Vitamin E, 30.0	30.0	Isopropanol, 39.0
Vitamin E, Acetate, 35.0	15.0	Ethanol, 78.5
Vitamin E Palmitate, 35.0	15.0	Ethanol, 78.5
Cod Liver Oil, 40.0	40.0	Isopropanol, 125.6

45 In each case, methyl methacrylate/ethylene glycol dimethacrylate macroporous crosslinked polymer beads containing the respective active ingredients in the following percentages are obtained.

Active Ingredient	%
Vitamin A	50
Vitamin D	50
Vitamin E	50
Vitamin E acetate	30
Vitamin E palmitate	30
Cod liver oil	50

**3.4.17 Example**

Three 0.4 gram portions of each of:

1. commercially available night cream;
- 5 2. the same commercially available night cream admixed with 1% vitamin E linoleate; and
3. the same commercially available night cream admixed with 1% polymer beads containing entrapped vitamin E linoleate (entrapped vitamin E linoleate equals 32% of the weight of beads), are rubbed onto three separate areas on a volunteer's lower arm. The viscoelastic properties of the treated skin of the arm were measured over a five minute period with an electrodynamicometer. The technique is described in detail in M.S. Christensen, C.W. Hargens III, S. Nacht, and E.H. Gans, J. Invest. Dermatol, 69 282 (1977).

The three areas are rubbed, applying equal pressure to each, after 15 and 24 hours. The results of the tests, in terms of percent increase in skin softening and release upon demand of the substances tested are measured.

The first compound is the commercially available night cream. It exhibits between a 25% and 30% increase in skin softening about one hour after application, increasing to about 40% skin softening approximately five hours after the initial application. Over the next 10 hours, its effectiveness rapidly declines to a 0% increase in skin softening. Rubbing the area to which the night cream was applied 15 hours after application has no effect.

The second compound is the night cream with admixed 1% vitamin E linoleate. It exhibits about a 40% increase in skin softening one hour after application, increasing to around 44% at five hours after application. It then drops to about a 15% increase over the next 10 hour period. Fifteen hours after application, the affected area is rubbed, causing the % increase in skin softening to remain level at 15% for nearly an hour before dropping to zero an hour later.

The third compound is the night cream with admixed 1% polymer beads that contain vitamin E linoleate, where the entrapped vitamin E linoleate is 32% of the weight of the beads. One hour after application, this compound exhibits between a 30% and 35% increase in skin softening. This increases to approximately 44% at the five hour mark. Over the next ten hours, this value declines to zero. By rubbing the skin area fifteen hours after the initial application, the increase in skin softening rapidly increases to between 20 and 25% over the next hour before declining to zero. Thus, a release of the active ingredient from the polymer beads can be effected at will by simply rubbing the area to which the beads were applied, even many hours after the initial application.

**3.4.18 Example**

35 A 2000 ml four-necked reaction flask equipped with a motorized stirrer, reflux condenser, thermometer, and nitrogen inlet was evacuated and purged with nitrogen. 1200 parts of deionized water, 9.6 parts of gum arabic and 9.6 parts of a sodium-based lignosulfonate available from Reed Lignins, Inc., under the trademark Marasperse N-22, were charged to the reaction flask. The mixture was heated, with stirring, in an oil bath at about 50 °C until the dispersants (gum arabic and lignosulfate) dissolved to form an aqueous phase.

To this mixture there was then added a freshly prepared solution of 90.5 parts of styrene (99.8% purity), 55 parts of commercial divinylbenzene (55.6% divinyl benzene, 42.3% ethylvinylbenzene), 2 parts of benzoyl peroxide (70% active ingredient and 30% water), and 69.4 parts of heptane. The aqueous phase and organic solution were agitated by stirring at a rate adjusted to give a plurality of droplets having an average droplet diameter of about 10-60 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400X) with the droplets being stabilized by the dispersants. This rate is approximately 1200 rpm. The reaction mixture was then heated to about 85 °C and maintained at that temperature for about 12 hours, at the previously adjusted stirring rate, to form porous beads of crosslinked styrene/divinylbenzene copolymer having heptane entrapped within the network of pores. The mixture was then cooled and the porous polymeric beads were removed from the reaction flask by filtration. The filtered beads were washed initially three times with one liter portions of deionized water to remove the dispersants, followed by three washes with one-liter portions of isopropanol to remove any residual, unreacted monomer and porogen. The beads were then dried in an oven at 80 °C for eight hours. The average particle diameter of these beads, which were white and opaque in appearance, indicating their macroporosity, was less than 35 microns, as measured by a Sedimentation Micromeritics Microsizer 5300, an instrument available from Micromeritics Instrument Company, Norcross, Georgia. The particle diameter determination method is described in detail in the "Microsizer 5300 Particle Size Analyzer Instruction Manual" (1984) associated with

the instrument.

The calculated or theoretical crosslinking density of the purified beads is 21.01%. This density is calculated by multiplying the weight of divinylbenzene (55 parts) by the purity of the divinylbenzene (55.6%) to get the actual weight of pure divinylbenzene which is then divided by the total weight of monomer (90.5 parts + 55 parts) and multiplied by 100.

The surface area of a sample of the purified beads was determined by the B.E.T. nitrogen multipoint analysis to be 38.41 m<sup>2</sup>/g while the pore volume was determined by the mercury intrusion method to be 0.206 cc/g. The B.E.T. method is described in detail in Brunauer, S., Emmet, P.H., and Teller, E., J. Am. Chem. Soc., 60, 309-16 (1938). The mercury intrusion method is described in detail in "Advanced Experimental Techniques in Powder Metallurgy," pages 225-252, (Plenum Press, 1970).

#### 3.4.19 Example

The procedure of Example 3.4.18 was repeated in every essential detail, except for the following: 750 parts of deionized water were used to dissolve 7.0 parts of gum arabic and 7.0 parts of Marasperse N-22 at about 23°C; 75 grams of styrene and 75 grams of divinylbenzene were used; 1.0 part of benzoyl peroxide and 65.03 parts of heptane were employed during polymerization and stirring was adjusted to give an average droplet diameter of below about 50 microns (rate approximately 800-1600 rpm); and three 300-ml portions of isopropanol were used to wash the beads. The macroporous crosslinked polymer beads obtained had the following characteristics:

Calculated Crosslinking Density, %:	27.8
Average Particle Diameter, microns:	25
Surface Area, m <sup>2</sup> /g:	59.43
Pore Volume, cc/g:	0.377

#### 3.4.20 Example

A two-liter four-necked reaction flask equipped as described in Example 1 was evacuated and purged with nitrogen. An aqueous phase made up of 600 parts of deionized water, 6.0 parts of gum arabic and 6.0 parts of Marasperse N-22 was added to the flask, and an organic solution made up of 72.0 parts of methyl methacrylate, 78.0 parts of ethylene glycol dimethacrylate, 2.0 parts of a 70% aqueous solution of benzoyl peroxide and 108.4 parts of toluene was dispersed in the aqueous phase with strong agitation (stirrer speed approximately 1000 rpm) to obtain a plurality of droplets having an average droplet diameter of below about 50 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400X), the droplets being stabilized by the dispersants.

The reaction mixture was then heated to 85°C and maintained at that temperature for 12 hours while maintaining a nitrogen flow of 2 ml/minute, to form porous beads of crosslinked methyl methacrylate/ethylene glycol dimethacrylate copolymer having toluene entrapped within the pores. The reaction mixture was then cooled and the beads collected by filtration, washed three times with 1000 part portions of water, and three times with 1000 part portions of isopropanol, then dried in air at 80°C for about 8 hours.

The calculated or theoretical crosslinking density of the purified beads is 52%, and was calculated by dividing the weight of ethylene glycol dimethacrylate (78.0 parts) by the total weight of monomer (150 parts), and then multiplying by 100.

The surface area of a sample of the purified beads is 98 m<sup>2</sup>/g and the pore volume is 0.36 cc/g, determined as described in Example 1 above.

#### 3.4.21-3.4.22 Examples

By repeating the procedure of Example 3.4.20 in every essential detail except for the weights of monomers employed, the macroporous crosslinked polymer beads described in the following table were obtained.



	Example 4	Example 5
Methyl Methacrylate, g	48.0	40.0
Ethylene Glycol Dimethacrylate, g	52.0	60.0
Calculated Crosslinking Density, %	51.0	58.8
Average Particle Diameter, microns	30	25
Surface Area, m <sup>2</sup> /g	92.70	95.07
Pore Volume, cc/g	0.366	0.368

### 3.4.23 Example

A 6-part portion of the macroporous crosslinked polymer beads prepared in Example 3.4.18 above is mixed at room temperature with 4 parts of retinoic acid (all-trans-form) dissolved in 10 ml of ethanol. The resulting suspension is hand-stirred for a few minutes, and the solvent is then allowed to evaporate to dryness in a fume hood at room temperature. The beads are calculated to contain 40% of retinoic acid retained within the pores.

### 3.4.24 Example

A 10-part portion of the macroporous crosslinked polymer beads prepared in each of Examples 3.4.19 through 3.4.22 is mixed at room temperature with 4 parts of retinoic acid (all-trans-form) dissolved in a solution of 8 parts of isopropyl myristate and 8 parts of isopropanol. The resulting suspension is hand-stirred and the solvent is then allowed to evaporate. The beads are calculated to contain 18.2% of retinoic acid and 36.4% of isopropyl myristate retained within the pores.

## 3.5 Counterirritants

Counterirritants which may be utilized in accordance with the present invention include any of the wide variety of substances known to have counterirritant properties. This extends to both liquids and solids, the solids being dissolved in a suitable solvent to form liquid solutions prior to their use in the present invention. While these substances vary widely in chemical and physical nature, some of the best known examples are as follows: camphor and its homologues, menthol and its homologues, thymol and its homologues, and like substances, e.g. other terpenes and terpene-like materials, such as turpentine oil and pine oil, salicylate esters, e.g., methyl salicylate, triethanolamine salicylate and glycol salicylates, salicylamide, allyl isothiocyanate, chloral hydrate, methyl nicotinate,  $\alpha$ -tocopheryl nicotinate, eucalyptus oil, capsicum preparations (capsaicin, capsicum and capsicum oleoresin), clove oil, histamine dihydrochloride and other substances which contain these materials, e.g., oil of wintergreen (containing methyl salicylate), peppermint oil (containing menthol), mustard oil (containing allyl isothiocyanate), and the like. Counterirritants are also used in the following mixtures:

- camphor and menthol;
- menthol and methyl salicylate;
- menthol and thymol;
- methyl nicotinate and methyl salicylate;
- turpentine and camphor;
- menthol, methyl salicylate and thymol;
- methyl salicylate, menthol and methyl nicotinate;
- methyl salicylate, camphor and menthol;
- menthol, methyl salicylate and eucalyptus oil;
- menthol, methyl salicylate and capsicum oleoresin;
- methyl nicotinate, capsicum oleoresin and dipropylene glycol salicylate;
- methyl salicylate, methyl nicotinate and capsicum oleoresin;
- camphor, menthol, methyl salicylate and capsicum;
- methyl salicylate, clove oil, menthol and eucalyptus oil;
- methyl salicylate, menthol, eucalyptus oil and turpentine oil;

methyl salicylate, menthol, camphor and methyl nicotinate;  
 methyl salicylate, thymol, eucalyptus oil and menthol;  
 methyl salicylate, menthol, camphor, eucalyptus oil and mustard oil;  
 methyl salicylate, menthol, camphor, monoglycol salicylate and methyl nicotinate;  
 5 methyl salicylate, capsicum, camphor, menthol and methyl nicotinate;  
 camphor, menthol, methyl salicylate, mustard oil and glycol monosalicylate; and  
 turpentine oil, pine oil, camphor, methyl salicylate and capsicum oleoresin.

Counterirritants of particular interest in the present invention are menthol, camphor and methyl salicylate.

10 Examples of organic solvents in which such substances can be dissolved to facilitate absorption include liquid petrolatum, petroleum ether, ethanol (especially for menthol and thymol) higher alcohols (especially for camphor), isopropyl myristate, diisopropyl adipate, and mineral oil. The solvent can then be evaporated or, if desired, retained together with the absorbed substance within the pores. Other formulating materials, such as carriers or adjuvants and the like can also be present, and will be incorporated into and onto the  
 15 beads together with the counterirritants and any other materials present.

### 3.5.1 Example

20 A 2000 ml four-necked reaction flask equipped with a motorized stirrer, reflux condenser, thermometer, and nitrogen inlet was evacuated and purged with nitrogen. 800 parts of deionized water, 6.4 parts of gum arabic and 6.4 parts of a sodium-based lignosulfonate available from Reed Lignins, Inc., under the trademark marasperse N-22, were charged to the reaction flask. The mixture was heated, with stirring, in an oil bath at about 50 °C until the dispersants (gum arabic and lignosulfate) dissolved to form an aqueous  
 25 phase.

To this mixture there was then added a freshly prepared solution of 102.3 parts of styrene (99.8% purity), 85.6 parts of commercial divinylbenzene (55.6% divinyl benzene, 42.3% ethylvinylbenzene), 5.3 parts of benzoyl peroxide (70% active ingredient and 30% water), and 130 parts of heptane. The aqueous phase and organic solution were agitated by stirring at a rate adjusted to give a plurality of droplets having  
 30 an average droplet diameter of about 10-60 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400X) with the droplets being stabilized by the dispersants. This rate is approximately 1200 rpm. The reaction mixture was then heated to about 80 °C and maintained at that temperature for about 20 hours, at the previously adjusted stirring rate, to form porous beads of crosslinked styrene/divinylbenzene copolymer having heptane entrapped within the network of pores. The  
 35 mixture was then cooled, diluted with 200 parts of water, and the porous polymeric beads were removed from the reaction flask by filtration. The filtered beads were washed initially three times with one liter portions of deionized water to remove the dispersants, followed by three washes with 0.6 liter portions of isopropanol: acetone mixture (7:3, respectively, by weight) to remove any residual, unreacted monomer and the heptane used as the porogen during polymerization. The beads were then dried in an oven at 80-100 °C  
 40 for eight hours. The average particle diameter of these beads was 25 microns, as measured by a Sedimentation Micromeritics Microsizer 5300, an instrument available from Micromeritics Instrument Company, Norcross, Georgia. The particle diameter determination method is described in detail in the "Microsizer 5300 Particle Size Analyzer Instruction Manual" (1984) associated with the instrument.

The calculated or theoretical crosslinking density of the purified beads is 25%. This density is  
 45 calculated by multiplying the weight of divinylbenzene (85.6 parts) by the purity of the divinylbenzene (55.6%) to get the actual weight of pure divinylbenzene which is then divided by the total weight of monomer (85.6 parts + 102.3 parts) and multiplied by 100.

The surface area of a sample of the purified beads was determined by the B.E.T. nitrogen multipoint analysis to be 91.2 m<sup>2</sup>/g while the pore volume was determined by the mercury intrusion method to be 1.0  
 50 cc/g. The B.E.T. method is described in detail in Brunauer, S., Emmet, P.H., and Teller, E., J. Am. Chem. Soc., 60, 309-16 (1939). The mercury intrusion method is described in detail in "Advanced Experimental Techniques in Powder Metallurgy," pages 225-252, (Plenum Press, 1970).

**3.5.2-3.5.3 Examples**

By repeating the procedure of Example 3.5.1 in every essential detail, except for the weights of monomers and porogen employed, porous crosslinked polymer beads were obtained having the following characteristics listed in Table 3.5.1:

TABLE 3.5.1

PORE CHARACTERISTICS OF DRY BEADS FROM STYRENE/DIVINYLBENZENE					
Example	Porogen	Proportions: Styrene/DivinylBenzene/Porogen	Average Particle Diameter (microns)	Surface Area (m <sup>2</sup> /g)	Pore Volume (cc/g)
2	Mineral Oil	100/89/180	25	75	1.36
3	Toluene	85.6/102.3/188	25	1.8	0.04

**3.5.4 Example**

A two-liter four-necked reaction flask equipped as described in Example 3.5.1 was evacuated and purged with nitrogen. An aqueous phase made up of 800 parts of deionized water, 8 parts of gum arabic and 8 parts of Marasperse N-22 was added to the flask, and an organic solution made up of 100 parts of methyl methacrylate, 100 parts of ethylene glycol dimethacrylate, 10 parts of butyl methacrylate, 2 parts of lauroyl peroxide and 173 parts of toluene was dispersed in the aqueous phase with strong agitation (stirrer speed approximately 1000 rpm) to obtain a plurality of droplets having an average droplet diameter of below about 50 microns, as determined by visual observation of a sample of the droplets being stabilized by the dispersants.

The reaction mixture was then heated to 80°C and maintained at that temperature for 6 hours while maintaining a nitrogen flow of 1 ml/minute, to form porous beads of crosslinked methyl methacrylate/butyl methacrylate/ethylene glycol dimethacrylate terpolymer having toluene entrapped within the pores. The reaction mixture was then cooled and the beads collected by filtration, washed three times with 1000 parts of water, and three times with 1000 parts of isopropanol, then dried in air at room temperature.

The calculated or theoretical crosslinking density of the purified beads is 47.6%, and was calculated by dividing the weight of ethylene glycol dimethacrylate (100 parts) by the total weight of monomer (210 parts), and then multiplying by 100.

The surface area of a sample of the purified beads is 52 m<sup>2</sup>/g and the pore volume is 0.4 cc/g, determined as described in Example 1 above.

**3.5.5-3.5.8 Examples**

By repeating the procedure of Example 3.5.4 in every essential detail except for the weights of monomers employed and, in one case, the porogen used, the porous crosslinked polymer beads described in Table 3.5.2 below were obtained.

TABLE 3.5.2

PORE CHARACTERISTICS OF DRY BEADS FROM METHYL METHACRYLATE (MMA) AND ETHYLENE GLYCOL DIMETHACRYLATE (EGDMA)					
Example	Porogen	Proportions: MMA/EGDMA/Porogen	Average Particle Diameter (microns)	Surface Area (m <sup>2</sup> /g)	Pore Volume (cc/g)
5	toluene	100/100/173	25	73.8	0.405
6	toluene	150/150/450	15	85.8	0.508
7	toluene	100/100/200	25	84.0	0.38
8	heptane	210/90/200	15	2.34	0.58

**3.5.9-3.5.15 Examples**

In these examples, preformed dry polymer beads from Examples 3.5.1 through 3.5.5 were impregnated with counterirritants or counterirritant solutions at specified proportions by combining the beads and counterirritant (or its solution), then mixing the resulting wet powder until it was homogeneous. In all cases except Example 3.5.12, the beads and counterirritant were combined and mixed at room temperature. In Example 3.5.12, the menthol, which is solid at room temperature, was first melted to liquid form by heating to 80 °C, which temperature was maintained as the compounds were combined and mixed. Counterirritant contents of the finished products in all cases including Example 3.5.12 were then determined by extraction and analysis according to conventional techniques. The materials, proportions, and final counterirritant contents are listed in Table 3.5.3. Example 3.5.15 is a prophetic example.

TABLE 3.5.3

IMPREGNATED PARTICLES - PREPARATION AND ANALYSIS				
Example	Example From Which Beads Were Taken	Counterirritant Solution (Weight %)	Weight Ratio, Beads to Solution	Counterirritant Level in Product (Weight %)
3.5.9	1	33% menthol in isopropyl myristate	1:1	16.7
3.5.10	2	33% menthol in diisopropyl adipate	1:1	18.7
3.5.11	3	41.7% menthol in mineral oil	1:1	20.8
3.5.12	4	100% menthol	3:2.45	44.8
3.5.13	5	50% menthol in ethanol	1:1	26.0
3.5.14	1	30% camphor in isopropyl myristate	6:4	12.0
3.5.15	1	100% methyl salicylate	6:4	40.0

### 3.5.16 Example

5 A two-liter four-necked reaction flask equipped as described in Example 3.5.1 was evacuated and purged with nitrogen. An aqueous solution made of 800 parts of deionized water, 8 parts of gum arabic and 8 parts of Marasperse N-22 was added to the flask, and an organic solution made up of 120 parts of methyl methacrylate, 80 parts of ethylene glycol dimethacrylate, 10 parts of butyl methacrylate, 100 parts of menthol, 100 parts of mineral oil and 2 parts of lauroyl peroxide was dispersed in the aqueous phase were  
 10 agitated by stirring at a rate adjusted to give a plurality of droplets having an average droplet diameter of about 10-80 microns. The reaction mixture was then heated to about 78°C and maintained at that temperature for about 20 hours, to form porous beads of crosslinked methyl methacrylate/butyl methacrylate/ethylene glycol dimethacrylate terpolymer having mineral oil and menthol entrapped within the pores. The mixture was then cooled, diluted with 200 parts of water, and the porous polymeric beads were  
 15 removed from the reaction flask by filtration. The filtered beads were washed three times with one liter portions of deionized water to remove the dispersants. The beads were then dried in air at room temperature.

The calculated or theoretical crosslinking density of the resulting polymeric beads was 38%, and was calculated by dividing the weight of ethylene glycol dimethacrylate (80 parts) by the total weight of  
 20 monomer (210 parts), and then multiplying by 100.

The surface area of a sample of the purified beads was 1.076 m<sup>2</sup>/g and the pore volume was 0.869 cc/g, determined as described in Example 1 above.

### 25 3.6 Epidermal Lipid Replacement Substances

Squalene, and in certain systems squalene as well, may be used as the porogen in a oneDstep procedure. With squalene, the steps must be performed under an inert atmosphere such as nitrogen. If a polymerization catalyst is used, it must be one which does not oxidize squalene. Azo catalysts are  
 30 examples of such catalysts. Also, polymerization temperatures are best held within a moderate range. In the case of squalene, on the other hand, such restrictions are generally less restrictive or not required.

### 3.6.1 Example

35 A 2000 ml four-necked reaction flask equipped with a motorized stirrer, reflux condenser, thermometer, and nitrogen inlet was evacuated and purged with nitrogen. 800 parts of deionized water, 6.4 parts of gum arabic and 6.4 parts of a sodium-based lignosulfonate available from Reed Lignins, Inc., under the trademark Marasperse N-22, were charged to the reaction flask. The mixture was heated, with stirring, in an  
 40 oil bath at about 50°C until the dispersants (gum arabic and lignosulfate) dissolved to form an aqueous phase.

To this mixture there was then added a freshly prepared solution of 102.3 parts of styrene (99.8% purity), 85.6 parts of commercial divinylbenzene (55.6% divinyl benzene, 42.3% ethylvinylbenzene), 5.3 parts of benzoyl peroxide (70% active ingredient and 30% water), and 130 parts of heptane. The aqueous  
 45 phase and organic solution were agitated by stirring at a rate adjusted to give a plurality of droplets having an average droplet diameter of about 10-60 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400X) with the droplets being stabilized by the dispersants. This rate is approximately 1200 rpm. The reaction mixture was then heated to about 80°C and maintained at that temperature for about 20 hours, at the previously adjusted stirring rate, to form porous beads of  
 50 crosslinked styrene/divinylbenzene copolymer having heptane entrapped within the network of pores. The mixture was then cooled, diluted with 200 parts of water, and the porous polymeric beads were removed from the reaction flask by filtration. The filtered beads were washed initially three times with one liter portions of deionized water to remove the dispersants, followed by three washes with 0.6 liter portions of  
 55 isopropanol:acetone mixture (7:3, respectively, by weight) to remove any residual, unreacted monomer and the heptane used as the porogen during polymerization. The beads were then dried in an oven at 80-100°C for eight hours. The average particle diameter of these beads was 25 microns, as measured by a Sedimentation Micromeritics Microsizer 5300, an instrument available from Micromeritics Instrument Company, Norcross, Georgia. The particle diameter determination method is described in detail in the

"Microsizer 5300 Particle Size Analyzer Instruction Manual" (1984) associated with the instrument.

The calculated or theoretical crosslinking density of the purified beads is 25%. This density is calculated by multiplying the weight of divinylbenzene (85.6 parts) by the purity of the divinylbenzene (55.6%) to get the actual weight of pure divinylbenzene which is then divided by the total weight of monomer (85.6 parts + 102.3 parts) and multiplied by 100.

The surface area of a sample of the purified beads was determined by the B.E.T. nitrogen multipoint analysis to be 91.2 m<sup>2</sup>/g while the pore volume was determined by the mercury intrusion method to be 1.0 cc/g. The B.E.T. method is described in detail in Brunauer, S., Emmet, P.H., and Teller, E., J. Am. Chem. Soc., 60, 309-16 (1938). The mercury intrusion method is described in detail in "Advanced Experimental Techniques in Powder Metallurgy," pages 225-252, (Plenum Press, 1970).

### 3.6.2 Example

A two-liter four-necked reaction flask equipped as described in Example 3.6.1 was evacuated and purged with nitrogen. An aqueous phase made up of 600 parts of deionized water, 6.0 parts of gum arabic and 6.0 parts of Marasperse N-22 was added to the flask, and an organic solution made up of 72.0 parts of methyl methacrylate, 78.0 parts of ethylene glycol dimethacrylate, 2.0 parts of benzoyl peroxide and 108.4 parts of toluene was dispersed in the aqueous phase with strong agitation (stirrer speed approximately 1000 rpm) to obtain a plurality of droplets having an average droplet diameter of below about 50 microns, as determined by visual observation of a sample of the droplets with an optical microscope (400X), the droplets being stabilized by the dispersants.

The reaction mixture was then heated to 85° C and maintained at that temperature for 12 hours while maintaining a nitrogen flow of 2 ml/minute, to form porous beads of crosslinked methyl methacrylate/ethylene glycol dimethacrylate copolymer having toluene entrapped within the pores. The reaction mixture was then cooled and the beads collected by filtration, washed three times with 1000 parts of water, and three times with 1000 parts of isopropanol, then dried in air at 80° C for about 8 hours.

The calculated or theoretical crosslinking density of the purified beads is 52%, and was calculated by dividing the weight of ethylene glycol dimethacrylate (78.0 parts) by the total weight of monomer (150 parts), and then multiplying by 100.

The surface area of a sample of the purified beads is 96 m<sup>2</sup>/g and the pore volume is 0.36 cc/g, determined as described in Example 1 above.

### 3.6.3 Example

Ten-part portions of preformed dry polymer beads from Examples 3.6.1 and 3.6.2 were each mixed at room temperature with a ten-part portion of an 67% solution of squalene in hexane. The resulting suspensions were hand-stirred for a few minutes. The hexane was then allowed to evaporate from the resulting wet powders at room temperature. The resulting beads contained 40% squalene-entrapped within their macropores.

### 3.6.4 Example

The procedure of Example 3.6.3 was repeated in every detail except for the following: two ten-part portions of the preformed beads prepared as described in each of Examples 3.6.1 and 3.6.2 were used, with one of the portions of the beads from each example being admixed with a ten-part portion of an 67% solution of squalene in hexane, and with the other two portions of beads being admixed with ten-part portions of an 67% solution of 50:50 mixture of squalene and squalane in hexane. In all four cases, the beads contained 40% of the absorbed, entrapped impregnant or impregnant mixture within their micropores.

### 3.6.5 Example

A two-liter four-necked reaction flask equipped as described in Example 3.6.1 was evacuated and purged with nitrogen. A mixture made up of 900 parts of deionized water, 7.2 parts of gum arabic, and 7.2 parts of Marasperse N-22 was charged to the flask. The mixture was heated with stirring in an oil bath at about 50°C until the dispersants (the gum arabic and the lignosulfonate) dissolved, to form an aqueous phase.

To this mixture there was then added a freshly prepared solution of 71 parts styrene (99.8% purity), 84 parts of commercial divinylbenzene (55.6% divinylbenzene and 42.3% ethylvinylbenzene), 7.0 parts of benzoyl peroxide (70% active ingredient, 30% water) and 135 parts of squalane. The aqueous and organic phases were agitated by stirring at a rate adjusted to give a plurality of droplets having an average droplet diameter of about 10-60 microns, as determined by visual observation of a sample of the droplets with an optical microscope (100X), the droplets being stabilized by the dispersants. This rate was approximately 1200 rpm. The reaction mixture was then heated to about 89°C and maintained at that temperature for about 20 hours, at the previously adjusted stirring rate, to form porous beads of crosslinked styrene/divinylbenzene copolymer having squalane retained within the network of pores.

The mixture was then cooled, diluted with 200 parts of water, and the porous polymeric beads were removed from the reaction flask by filtration. The filtered beads were washed three times with one-liter portions of deionized water to remove the dispersants. The beads were then dried in air at room temperature.

The calculated or theoretical crosslinking density of the resulting polymeric beads was 30%, and was calculated by multiplying the weight of divinylbenzene (84 parts) by the purity of the divinylbenzene (55.6%) to get the actual weight of pure divinylbenzene which was then divided by the total weight of monomer (155 parts) and multiplied by 100.

The surface area of a sample of the purified beads was 0.88 m<sup>2</sup>/g and the pore volume was 1.15 cc/g, determined as described in Example 3.6.1 above. Analysis for squalane indicated that the squalane content of the finished product was 41.8% by weight.

The foregoing description is directed primarily to preferred embodiments and practices of the present invention. It will be readily apparent to those skilled in the art that further changes and modifications in the actual implementation of the concepts described herein can be made without departing from the spirit and scope of the invention as defined by the following claims.

### Claims

1. A topical composition comprising solid particles containing a substantially continuous non-collapsible network of pores open to the exterior of said particles, and an impregnant retained inside said pores, wherein said impregnant comprises one or more of: a hair growth promotion agent; a therapeutic agent effective in the cosmetic and/or therapeutic treatment of acne; a fragrant substance; one or more substances selected from vitamins, vitamin derivatives and vitamin-containing substances; a counter-irritant substance; an epidermal lipid-replacement agent; optionally in a solvent.
2. A topical composition in accordance with claim 1 in which said solvent is a member selected from the group consisting of ethers, alcohols, aromatics and alkanes.
3. A topical composition in accordance with claim 1 or 2 in which said impregnant comprises a hair growth promotion agent which is Minoxidil.
4. A topical composition in accordance with any preceding claim in which said impregnant comprises a therapeutic agent for acne selected from benzoyl peroxide, salicylic acid, resorcinol, and mixtures thereof.
5. A topical composition in accordance with any preceding claim in which said impregnant comprises a fragrant substance selected from flower oils, essential oils, animal substances synthetic fragrances and resinoids.
6. A topical composition in accordance with any preceding claim in which said impregnant is comprised of a retinoid composition, preferably selected from retinol, 3-dihydroretinol, retinoic acids, retinoic aldehydes, retinoic acid esters, and aromatic derivatives thereof.
7. A topical composition in accordance with any preceding claim in which said impregnant comprises a counterirritant substance which is a liquid substantially immiscible with water and/or is in the form of a solution of a counterirritant compound in a solvent substantially immiscible with water or in a solvent at least partially miscible with water; the solution optionally being an organic solution of a counterirritant compound which is solid under ambient conditions.



8. A topical composition in accordance with any preceding claim in which said impregnant comprises a counterirritant substance comprised of a volatile compound, preferably selected from menthol, camphor and methyl salicylate.

9. A topical composition in accordance with any preceding claim in which said impregnant comprises an epidermal lipid replacement agent selected from squalane, squalene, and mixtures thereof.

10. A topical composition in accordance with any preceding claim in which said solid particles are substantially spherical in shape, are formed from a cross-linked polymer, have an average diameter of about 10 microns to about 40 microns, have a total pore volume of about 0.1 cc/g to about 2.0 cc/g have a surface area of about 20 m<sup>2</sup>/g to about 200 m<sup>2</sup>/g, and have an average pore diameter of about 0.003 micron to about 1.0 micron.

11. A topical composition in accordance with any preceding claim in which said solid particles are formed of a copolymer of styrene and divinylbenzene; or of methyl methacrylate and ethylene glycol dimethacrylate or of 4-vinylpyridine and ethylene glycol dimethacrylate.

12. A topical composition in accordance with any preceding claim in which said solid particles are combined with a vehicle to form a composition selected from fluid, semi-solid and solid compositions.

13. A topical composition in accordance with any preceding claim in which said impregnant comprises from about 5% to about 65% thereof.

14. A method for preparing a topical composition according to any preceding claim comprising:

(a) combining a monomer composition capable of forming a crosslinked polymer with an impregnant to form a homogeneous, substantially non-water-miscible liquid solution;

(b) dispersing said non-water-miscible liquid solution in an aqueous phase to form a suspension containing said non-water-miscible liquid solution as discrete droplets;

(c) polymerizing said monomer composition in said suspension under conditions under which said impregnant is substantially inert to convert said droplets to solid particles containing a non-collapsible, substantially continuous network of pores open to the exterior of said solid particles with said impregnant retained in said pores; and

(d) recovering said solid particles from said aqueous phase.

15. A method for preparing a topical composition according to any of claims 1 to 13 comprising:

(a) forming solid particles containing a substantially continuous network of pores open to the exterior of said particles; and

(b) impregnating said pores of said solid particles with an impregnant.

16. A method in accordance with claim 15 in which step (a) comprises:

(i) combining a monomer composition with a substantially water-immiscible liquid species which is inert with respect to said monomer composition to form a homogeneous, substantially water-immiscible liquid solution;

(ii) suspending said liquid solution in an aqueous solution to form a dispersion;

(iii) polymerizing said monomer composition in said dispersion to form solid beads containing said water-immiscible liquid chemical species;

(iv) recovering said solid beads from said dispersion; and

(v) extracting said water-immiscible liquid chemical species from said solid beads.

17. A method for cosmetic treatment of an epidermal region, said method comprising applying to said epidermal region a topical composition according to any of claims 1 to 13, said impregnant comprising a cosmetic treatment agent.

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54 Controlled release formulations.

57 Active substances intended for topical application are incorporated in novel formulations in which they are retained as impregnants inside the pores of porous solid particles or microspheres. The pores form a continuous network open to the exterior of the particles, permitting outward diffusion of the impregnants at a controlled rate depending on the pore size. The impregnated particles are prepared by the polymerization of monomer droplets which contain the active substance mixed in with the monomers, or by impregnation of preformed particles with the active substance.

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# EUROPEAN SEARCH REPORT

Application Number

EP 88 30 7947

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
P,X	US-A-4 690 825 (WON) * Claims; column 2, lines 31-34; column 3, lines 55-65; column 4, line 2; column 6, lines 29-31 * ----	1,2,5,7 8,10-17	A 61 K 9/22 A 61 K 7/00 A 61 K 7/46 A 61 K 9/50
X	EP-A-0 143 608 (ALLIED COLLOIDS) * Claims; page 6, lines 1-3,29-31; page 7, lines 14-21; page 9, lines 10-25 * ----	1,2,5, 10-17	
X	FR-A-2 352 547 (VIRIDIS) * Claims 1-3; page 2, lines 24-27; page 3, lines 30-34; page 6, example 1 * -----	1,2,5,9 -17	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 10-03-1989	Examiner SCARPONI U.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	

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